

IMPACT OF CONTACT TRACING ON INCIDENCE OF TUBERCULOSIS
IN SOUTH AFRICA: A MATHEMATICAL MODELING STUDY

by

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ABSTRACT

South Africa has a high incidence of tuberculosis (TB) and is ranked among the top 30 countries with high incidence of the disease according to the Global Tuberculosis Report released by the World Health Organization in 2019. There is an urgent need to consider ways in which incidence of TB can be reduced so that South Africa can meet the WHO End TB Strategy targets. The problem in South Africa is compounded by the high prevalence of human immunodeficiency virus infections (HIV). Prevalence surveys have shown at least one-third cases with TB can go undetected thus contributing significantly to the disease burden by transmitting this infection to others. Contact tracing is one method which can control this mode of spread by tracing close contacts of patients actively and testing them. Cluster randomized trials have been inconclusive on contact tracing prompting this modeling study.

A compartmental mathematical model in continuous time of TB in South Africa was simulated and stratified by HIV and age, till 2019. Contact tracing was then simulated in the settings where three factors were varied: a) the average infectious duration for an undetected case of TB, b) the proportion of incident cases which were found among contacts and c) percentage of contacts with active TB who were traced and treated. The reduction in incidence with these interventions was compared to the reduction which would be achieved if current trends in TB in South Africa continued without any interventions.

The results showed that as the proportion of contacts among incidence TB patients increased, the average duration time of being infectious decreased from 3 months to 6 months and as proportion of contacts covered in the intervention increased, the intervention was more effective.

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As I come to the culmination of my Masters in Science course here at Hopkins, I am overwhelmed with gratitude as I looked back at all the good gifts I have enjoyed over the last couple of years.. I have no business being here and studying here and yet here I am. As I submit my thesis, I would like to thank the most important people on this page as I don't think I will ever get the chance. It is a pity, because their contribution cannot be summarized in a few sentences, but I guess, that cannot be helped. So here goes.

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INTRODUCTION

Tuberculosis (TB) is the leading cause of death globally from a single infectious agent and among the top 10 causes of deaths worldwide (1). In 2018, there were an estimated 10 million new cases of tuberculosis globally with 1.5 million people dying due to the infection (1). One million (10%) of these were human immunodeficiency virus (HIV) positive. Globally, the incidence of TB has remained static since the turn of the 21st century with a 2% drop in incidence from 2000 – 2018 (1). The World Health Organization (WHO) End TB Strategy aims to reduce deaths due to TB by 95% and to reduce the incidence by 90 between 2015 and 2035 (2). As part of this strategy, the interim targets developed for 2020 are to reduce deaths due to TB by 35% and incidence by 20%, and for 2025 the target reduction in deaths is 75% and target reduction in the incidence is 50% (2). To meet the 2020 targets for End TB, the drop in incidence must equal 4-5% per year which may not be possible given current reductions in incidence and mortality (1).

TB in South Africa is still a substantial problem which is further exacerbated by HIV. In 2018, three percent of the global burden of new TB cases occurred in South Africa, with an incidence of 520 per 100,000 people, down from 759 per 100,000 in 2015 (1). 59% of TB cases occurred in people with HIV (PWH) (1). South Africa has the highest burden of HIV in the world with a total of 7.7 million PWH (3,4). While South Africa is on track to meet the End TB 2020 target of reducing incidence of TB cases by 20% from the 2015, the current drop in incidence rate may not guarantee that South Africa meets the 2035 goals for End TB Strategy i.e. 95% reduction in TB related deaths and a 90% reduction in TB incidence (2,3,5).

Most of the TB diagnosis is based on passive case finding (PCF) and treatment, wherein symptomatic patients present to the clinic of their own accord to be tested and if positive are treated. However, the

WHO estimates that one-third of the people with TB are not diagnosed and notified to public health authorities – an estimated 3.6 million globally in 2017 (4). Nationwide cluster surveys in the Gambia, Vietnam and Zimbabwe have demonstrated a high prevalence of sputum-positive tuberculosis among asymptomatic cases, underscoring the importance of active case finding (ACF) that does not rely entirely on symptoms (6–8). House to house surveys done in Korea, India and South Africa noted that the prevalence of TB increased when asymptomatic cases were tested using either sputum or X-ray and symptoms or sputum and X-ray, respectively. The Korean study had 5.4% detection rate (5000/92 000 examined) at health centers as compared with 2.1% (14000/659000) in the household surveys (9). House to house testing while inefficient detected three times more cases than healthcare centers. The study in India found that performing X-rays in TST positive populations detected TB at the same rate among those who underwent X-rays based on symptoms (10). In South Africa, the official notification figure for KwaZulu in 1974 was 177/100 000, compared to a prevalence of 804/100 000 estimated from the survey. So, there is a pool of undetected TB infected patients who could be contributing to disease spread because they are not diagnosed and treated early (11). According to the National Institute for Healthcare and Excellence (NICE) guidelines in UK 2016, “Active case finding is looking systematically for cases of active tuberculosis and latent infection in groups known, or thought to be, at higher risk of tuberculosis, rather than waiting for people to develop symptoms/signs of active disease and present themselves for medical attention (passive case finding)” (12).

However, information on impact of ACF from randomized controlled trials is mixed. Some studies have shown an increased rate of diagnosis with ACF while some have not shown the same results. In Brazil, a study that compared door-to-door testing versus education found a higher rate of diagnosis with the door to door testing arm (13). The DETECTB trial in Zimbabwe noted a higher diagnosis rate of TB in high TB prevalence communities in Harare, Zimbabwe (8). A cluster randomized trial in Vietnam by Fox

et al was done which demonstrated a higher incidence rate of tuberculosis among the arm which tested household contacts compared to the arm which employed only passive case finding (PCF) (14). The ZAMSTAR trial in Zambia and the Western province of South Africa was a 2X2 factorial design cluster randomized trial in a high burden area with also a high prevalence of HIV (15). This trial compared community interventions and investigation of household contacts to evaluate enhanced case detection and a change in the epidemiology of TB in the communities. While differences were not statistically significant, the authors did note higher case detection in the contact investigation arm ($p=0.06$), though no difference with community-based enhanced case finding. The reasons for no significant differences being detected as postulated by the authors were: a) heterogeneity of TB prevalence among the communities being investigated, b) distance between the sample collection and processing laboratories leading to denaturation of the samples and c) the fact that the cases who were detected may have already been infectious for a long duration and already have transmitted the infection to the others in the community. Irrespective of the statistical conclusions, there seems to be some benefit in screening for TB in high burden communities from this study which was the first randomized, factorial design which looked at not just case detection rates but the overall effect of ACF on the epidemiology of TB within communities (15). In a cluster randomized trial in South Africa, Hanrahan et al were unable to document a higher rate of detection among contacts with ACF (16). A systematic review on screening for TB revealed that there was an increase in the short-term detection of cases in most of these studies, while the long-term effects were less certain (17–19). One of the reasons for this could be that the studies were usually community-based trials and conducted ACF in the entire community (19).

Even though the results of cluster randomized trials are mixed, there is still some advantage to testing of household contacts. The fact that TB spreads through aerosol production should suggest that close exposure to patients with TB will increase the risk of being infected with TB. This has been shown in

studies which have looked exclusively at infection rates among contacts (19). Trials which compared ACF at the community level versus among contacts also have shown a higher diagnosis rate among contacts (14). If the targeted group is at a higher risk of developing TB, then ACF in these special populations may help in providing a higher yield of cases than if it was done in the general population. Studies have documented results where more than half of prevalent cases were undiscovered with PCF (15). There is also evidence that ACF detects cases earlier than PCF (15). Studies have not shown any improvement in mortality with ACF, though this is most likely due to survival bias. People are more likely to die without anti tuberculosis therapy and before diagnosis. And thus, the mortality rate among patients on treatment with anti TB therapy and detected by PCF may underestimate the true mortality (19,20). This may lead to an attenuation of the beneficial effect which is provided by ACF. Thus, the impact and implementation of ACF depend on four factors: 1) prevalence of the disease, 2) epidemiological importance, 3) chances of being detected otherwise and 4) cost (20). In areas of *high prevalence*, the disease burden is high as well as the proportion of undiagnosed TB cases. The individual's risk of getting infected is higher as compared to the general population. ACF may have benefit in these settings (20) *Epidemiological importance* is more concerned with a certain group or individuals and their effect on the community. Those with a higher burden of disease (HIV infected) and more likely to infect others should be diagnosed and treated early (20). If the patients have a *higher chance of getting tested* for TB, then ACF may not be very helpful. However, in areas with poor access to healthcare, where the chances of early detection are low, then ACF may be useful (20). Lastly, the cost of ACF must be considered with the incremental benefit expected from an increased detection in cases (21). Based on these factors i.e. high load of undiagnosed cases and the benefits of ACF in certain scenarios, the WHO now recommends ACF among contacts of tuberculosis patients in the context of high burden countries (18). To summarize, there is a high burden of active, infectious TB which is

undetected, and which needs to be diagnosed. Community level screening programs may not lead to a higher diagnosis rate of these people; however, a targeted screening and ACF strategy among contacts may lead to earlier and more comprehensive diagnosis with overall survival improvement as well as improvement in the transmission dynamics of TB. ACF may aid South Africa in achieving the End TB Strategy goals; however, the magnitude of benefit that might accrue to national incidence is unclear.

The current health system in South Africa is based on a district health system with 52 districts in 9 provinces and 3500 public healthcare facilities (22). Ninety percent of TB tests and most TB treatment is provided in the public health sector (22). Modelling studies in South Africa have also described the global trend which is two-thirds of cases being detected with 34% of cases with presumptive TB not having any record of testing or treatment (1,(13,23). This missing one-third therefore forms an important link in the spread of tuberculosis. Failure to address this 33% may lead to a loss in the gains made over the last 3 years. ACF may be one way to address this gap; current TB management in South Africa relies primarily on passive case detection: patients presenting with symptoms (16,24). The Kharitode study done by Hanrahan et al used an incentive-based strategy and a household-based strategy to test contacts of TB patients (16). They were unable to find a substantial increase in TB diagnoses and were unable to demonstrate a reduction in incidence of TB. One of the reason postulated was using Xpert MTB/RIF instead of cultures which were used by Fox et al in Vietnam (14). The Kharitode study may have failed to show effect because the diagnosis rates of Xpert MTB/RIF test would not have been as sensitive as cultures in picking up early stage of the disease among contacts (16). Other reason could have been that the communities may have needed more follow up time with the intervention to show a reduction in incidence -something that may not have been possible due to logistical factors (16). As SA has a high burden of TB, a high-risk subpopulation with HIV, and many undetected cases, widescale use of ACF still has the potential to substantially impact the SA TB epidemic. We therefore conducted a modeling

study to assess the impact of ACF on incidence of TB in South Africa and to see if it meets the End TB targets of 2030 by allowing the intervention to run for a longer duration of time.

2.METHODS

2.1 Model structure

We created a compartmental, continuous-time model of TB stratified by age and HIV status (Figure 1). We represented individuals as being in one of the following TB states: uninfected, latent TB within two years of infection (early latent state), latent TB greater than two years after infection (late latent state), active TB, and cured. We used age strata of 0-4, 5-14, 15-24, 25-34, 45-54, 55-64 and above 65 years old, as the prevalence of HIV and TB is different at the extremes of age (24). We used a simplified representation of the HIV continuum of care: HIV negative, HIV positive not on ART and HIV positive on ART as in a previous study of TB in South Africa (25).

With respect to TB, individuals who are infected move from the uninfected state to the early latent state; the probability of infection depends on individuals' age and HIV status as well as the prevalence of active TB in the total population. If these individuals do not reactivate, they progress to late latent TB after two years (26,27) . Individuals in either latent state reactivate at a rate that depends on their age and HIV status and is higher for early latent than for late latent TB. Once in the active state, individuals contribute to the force of TB infection. They can spontaneously recover, in which case they revert to the early latent state, or they can move to the recovered state with treatment, at a rate that depends on national treatment rates and the probability of treatment success.

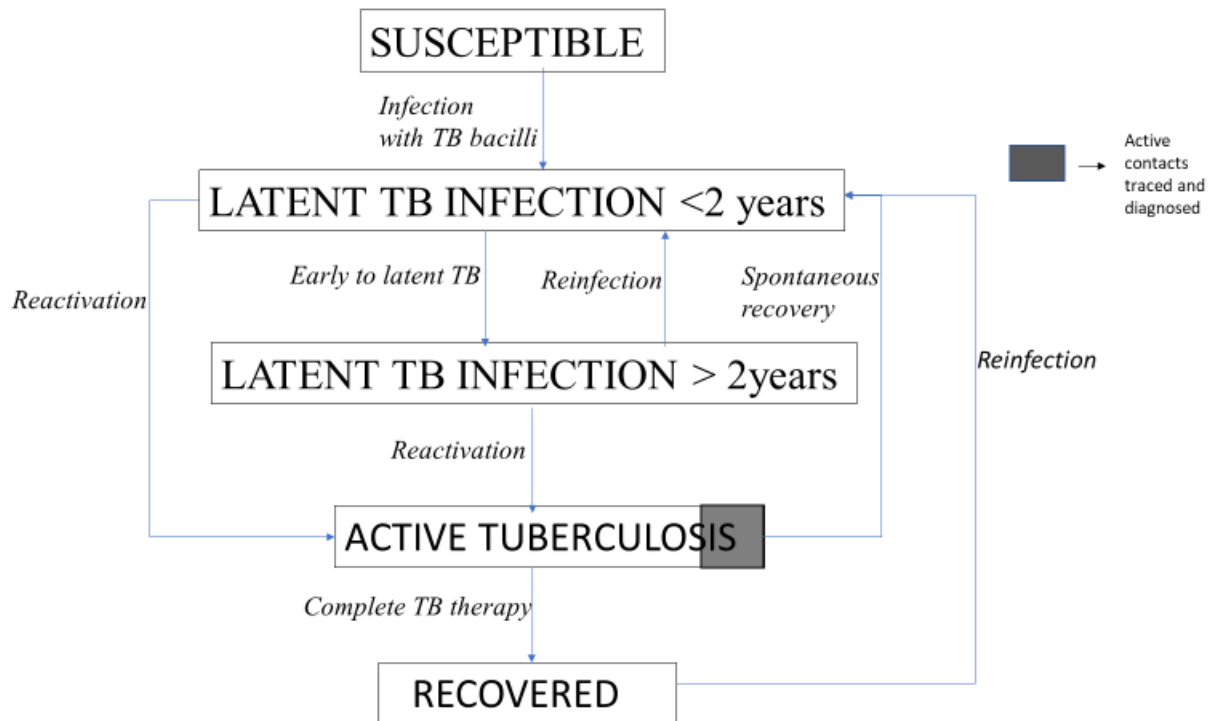
Individuals in both the late latent and recovered states can be re-infected and revert to the early latent state. With respect to HIV, a proportion of children are born HIV-positive due to maternal transmission; the remainder of births are HIV-negative. Once individuals have aged into adulthood (15 years old),

they are at risk for HIV acquisition. Newly infected individuals start in the HIV-positive not on ART state and move to the HIV-positive on ART state, at a rate that is consistent with national estimates of ART coverage (3). ART treated individuals may move back to the not on ART state. We did not model rates of HIV infection and ART initiation dynamically; instead we set them to historical rates and further tuned them to reproduce trends in HIV prevalence and ART coverage over the past two decades.

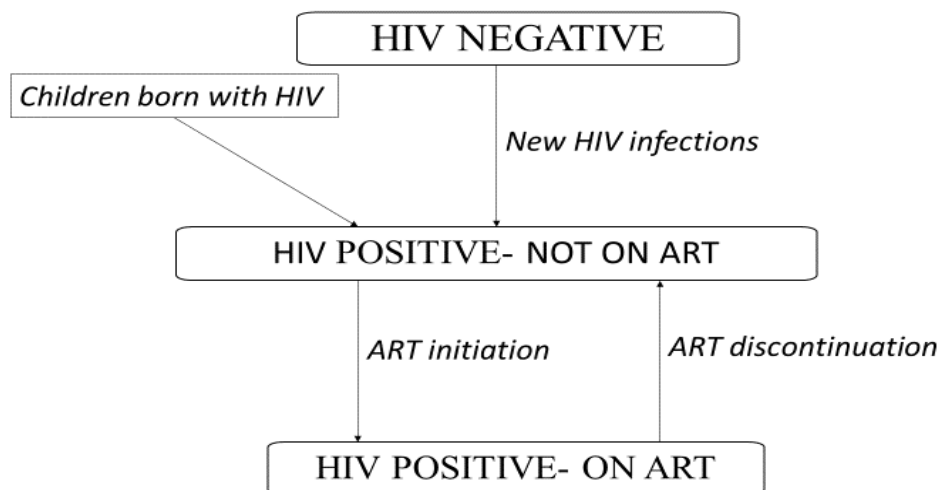
We modeled ACF by splitting up the Active cases compartment into two parts: one part was the proportion of new cases of TB among non-contacts and the other was the proportion of new cases of TB among contacts of TB patients who would be detected earlier by ACF strategy.

Figure 1: Model Structure

Model of TB transmission



Model of HIV:



2.2 Model parameters and data sources:

We replicated the demographic structure of South Africa's population by using age-specific mortality rates starting in 2006, the earliest year for which we could obtain age-stratified mortality rates (24). We reproduced the HIV epidemic by adjusting incidence; we used incidence rates and mother-to-child transmission going back to 1990 and then calibrated those rates to mimic current prevalence trends in South Africa (24). We assumed that all incident HIV in the 0-15 age group represented mother-to-child transmission (MTCT) and calibrated this process to WHO estimates (3). The ART discontinuation rates were obtained from cohort studies done by Asimwe et al (28). Mortality rates among the HIV infected population were obtained from comparative analysis done on HIV cohorts in sub-Saharan Africa by Zaba et al (29).

The compartmental model reduces to a set of ordinary differential equations. These equations were coded in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio 1.2.5033 and solved using the *deSolve* package (30)

Table1: Fixed model parameters:

Parameter	Point estimate	Range	Source
Treatment Proportion of anti-tuberculous treatment coverage in South Africa (2015)	76%	57 - 100	(31)
Success proportion with anti-TB therapy in HIV negative patients and those on ART	81%	72 – 87	(32)

Successful proportion of HIV positive patients not on ART treated with anti TB therapy	72%	64 – 79	(33)
Spontaneous recovery rate in HIV negative patients	0.058 per person-year	0.021 – 0.086	(34)
Rate of ART discontinuation	0.1411 per person-year	0.1406 – 0.1416	(35)
Rate of treatment of TB with passive testing	1.42 per person-year	0.71 – 2.99	(31)
Mortality Rate			
Case fatality ratio of TB	0.22	0.14-0. 30	(36)
Added Mortality in PWH on ART*	0.004 per person-year	0.0036 – 0.0044	(37)
Added Mortality in ART naive*	0.0203 per person-year	0.0200 – 0.0205	(38)
Latent protection factor**	0.28	0.21 – 0.39	(39)

*- This rate is applied only for HIV cases since 2018.

** - This implies that those with a latent TB infection are protected from reinfection by a factor of 0.28. i.e 28 out of 100 LTBI cases will be re-infected if re-exposed to TB as opposed to unexposed.

Table 2: Calibrated model parameters:

Tuberculosis Infection Rates (Relative Risk in each group)	
HIV negative, ≤15 years	7
HIV negative, >15 years	1 (ref)
HIV positive, >15 years	15
Reactivation Rates of tuberculosis	
<i>Early reactivation:</i>	
HIV negative, ≤15 years	3.6
HIV negative, >15 years	1 (Ref)
HIV positive, not on ART	32
<i>Late reactivation:</i>	

HIV negative, ≤ 15 years	3.6
HIV negative, > 15 years	1 (Ref)
HIV positive, not on ART	32
Mortality Rates in all HIV patients (per 100 person-years)- includes on ART and not on ART	
Rate projected from 1994 - 2000	1.2
Rate projected from 2000 - 2018	1
Rate projected 2018 onwards	0.15
Fraction of HIV positive births (per 1000 births)	
Rate projected from 1996 - 2017	7
Rate projected 2017 onwards	5.7
Annual Rate of HIV incidence (per 1000 person- years)	
Rate projected from 1990 projected to 2000	0.93
Rate projected from 2000 projected to 2010	13.9
Rate projected from 2010 projected to 2020	6
Rate projected 2020 onwards	4
ART initiation rate (per 1000 person -years)	
Rate projected from 2004 - 2010	1
Rate projected from 2010 - 2020	60
Rate projected 2020 onwards	340

The transmission and reactivation of TB in our model was governed by parameters described in Table 1 and Table 2. Most parameters were drawn from a review of the literature (Table 1), but we calibrated key parameters to replicate recent trends in the South Africa TB epidemic (Table 2).

2.3 Calibration process:

We calibrated the HIV incidence, mortality and treatment rates to mimic the current prevalence trends of HIV in South Africa, using empiric maximum likelihood estimation, in which we allowed 27 parameters to vary to see what combination of parameters yielded the maximum likelihood. Our likelihood function

was structured to reproduce the TB and HIV trends in South Africa over the past two decades, and was formulated as a product of three components:

- a) TB incidence – we represented the WHO-reported TB incidence from 1970 to 2018. We used the least square method to estimate this proportion where the sum of squares between the actual value and the simulated model value was minimized using the property of linear regression where in a normal distribution the maximum likelihood estimation is equal to the sum of least squares.
- b) HIV prevalence- we represented the WHO-reported HIV prevalence from 1990 to 2018 as a draw from independent normal distributions whose mean was the model-estimated incidence and whose standard deviation was the half of the confidence interval width divided by 1.96.
- c) Fraction of estimated HIV prevalent patients on ART- we used the WHO reported fraction of estimated HIV prevalent patients on ART. The figures are available from 2004 onward. We used the least square method to estimate this proportion where the sum of squares between the actual value and the simulated value was minimized.

2.4 Intervention

We modeled contact tracing as a reduction in the average time during which contacts with active TB were infectious. On an average based on current treatment initiation rates in South Africa, on an average a person can be infective for 8.5 months before being detected. If contact tracing is carried out then this duration should reduce and that is how we represented contact tracing in our model- by reducing the average infectious duration from 8.5 months to 3 and 6 months. In exploring the effects of contact tracing, we varied three parameters which can impact the effectiveness of contact training: (1) How much contact tracing reduces the time during which contacts are infectious, (2) what proportion of all incident TB cases are close contacts of other persons with active TB, and (3) what proportion of close contacts are screened and treated by the contact training intervention. We evaluated combinations of

these three parameters, for an average infectious duration time of 3 months and 6 months. Five values of the proportion of incident TB who are contacts (4.5%, 13%, 20%, 30% and 50%), and four values of the proportion of contacts reached by screening (25, 50, 75, and 100%). The values of 4.5% and 13% for proportion of incident TB cases who are contacts were based on ZAMSTAR and DETECTTB trials (8,15). The values of 20%, 30% and 50% were used to assess the impact in localized communities where the percentage of TB among contacts was higher. Our primary simulations assumed that the rates of TB transmission and reactivation, HIV incidence, and ART initiation remained constant after 2020. We tested the impact of these assumptions by performing two sets of sensitivity analyses. The first allowed four parameters to continue to change from 2020 to 2030 at the same rate they had changed in the previous 10 years. The second sensitivity analysis allowed the four parameters to change, but reach a value halfway between the 2020 value and the extrapolated 2030 value and the last allowed the four parameters to continue at the same rate as 2020 to 2030. The four parameters we tested this way were: a) reactivation rate, b) ART initiation rate, c) HIV incidence rate and d) force of infection of TB. We ran the sensitivity analysis assuming 13% of contacts among incident cases being discovered after an infectious duration time of 3 months.

3.1 RESULTS:

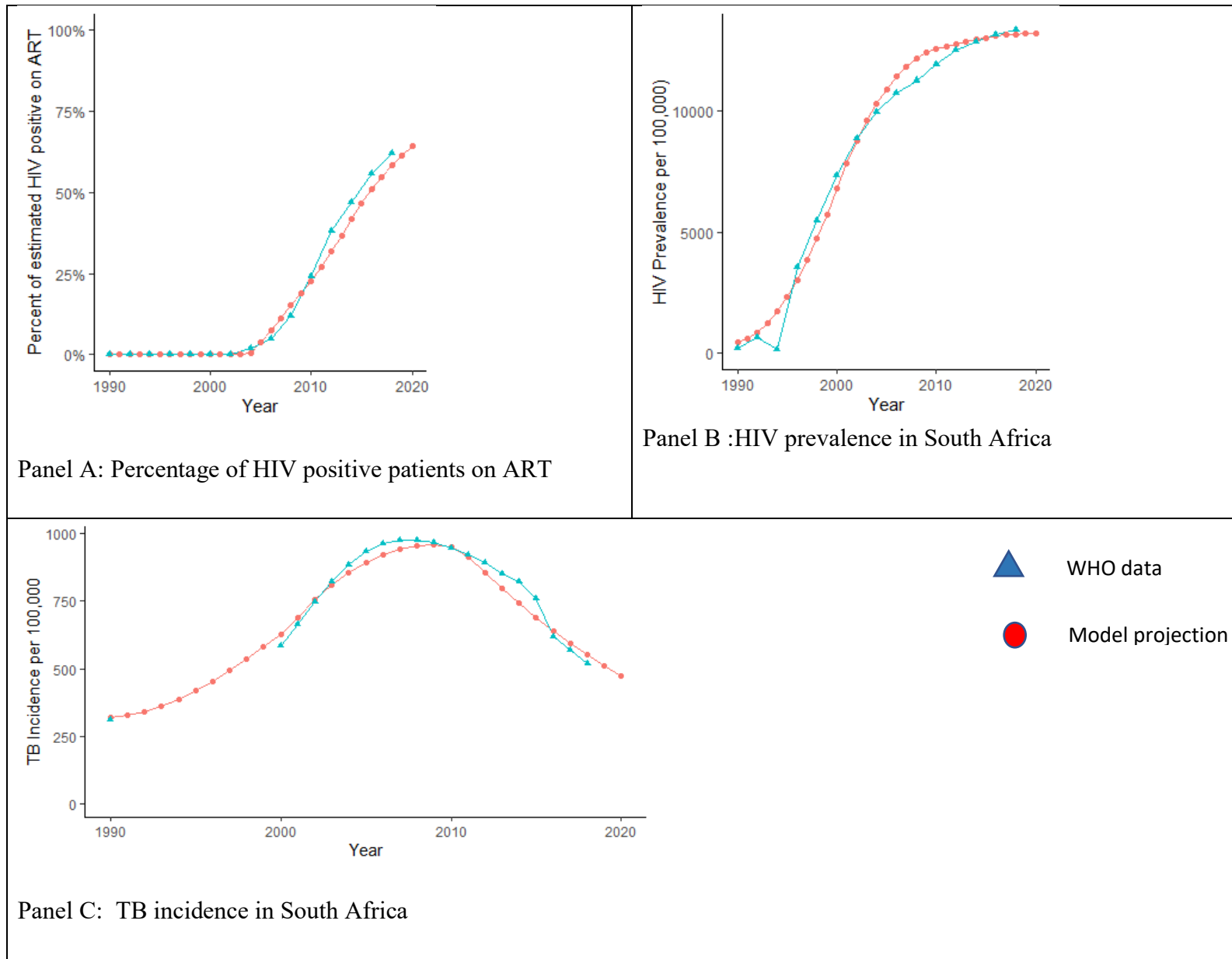
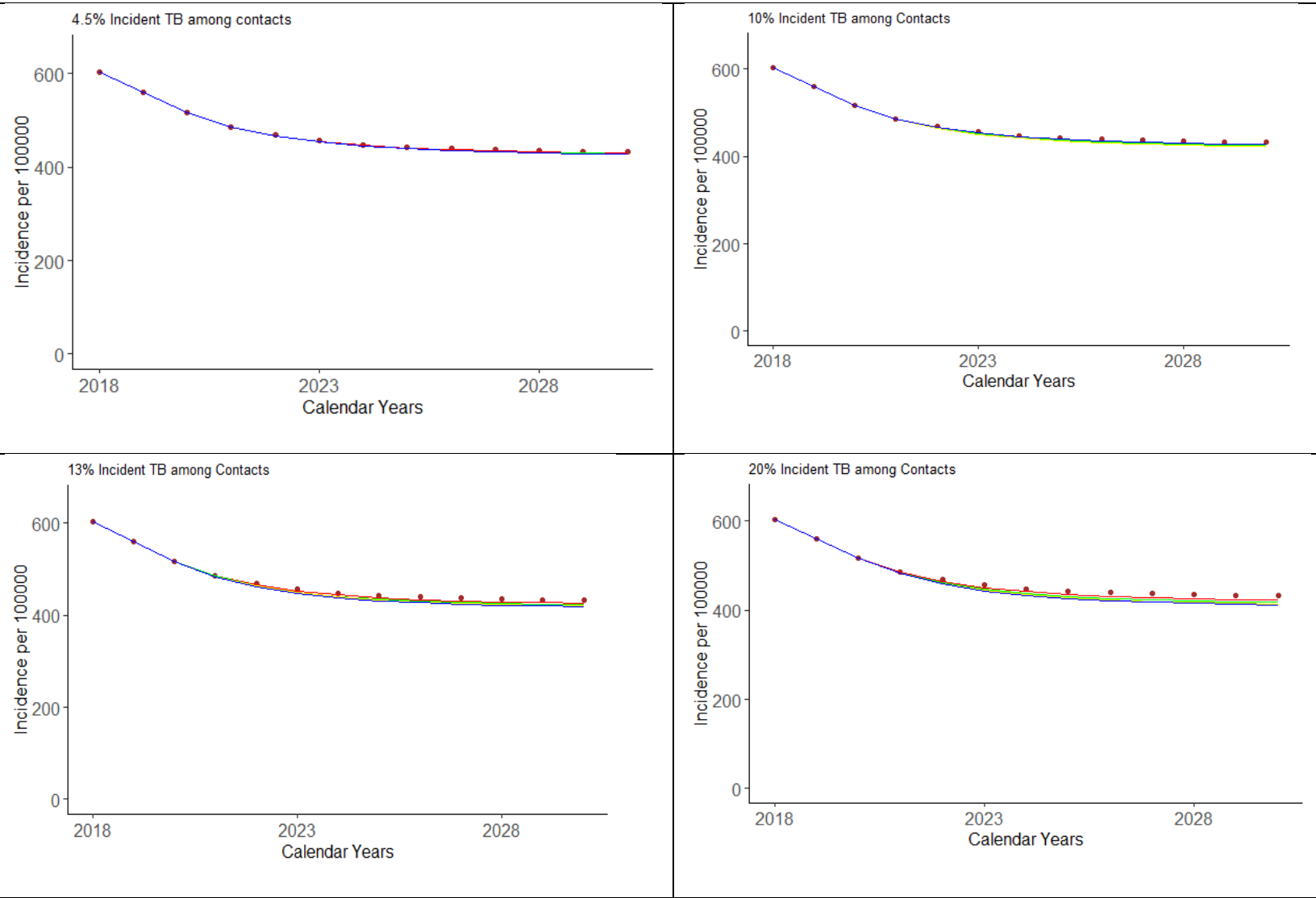


Figure 2: Calibration targets Panel A shows the percentage of patients who are on ART as per WHO data and that calibrated by our model Panel B shows the prevalence of HIV in South Africa as per data and calibrated by our model. Panel C shows the incidence of TB calibrated by our model as compared to WHO data. Red lines indicate our model projections while blue lines indicate the trends according to WHO data.

We first recreated HIV prevalence trends and the fraction of PWH on ART in South Africa. The prevalence of HIV was 13.3% (95% CI: 12.3 – 13.3) and the percentage of PWH on ART was 62% (95%CI: 57 – 66) according to 2018 WHO estimates (32) After this we recreated the TB incidence trends in South Africa and projected it to 2030.

Our model reproduced calibration targets well (Figure 2). In the absence of any interventions, our model projected that the incidence of tuberculosis in South Africa would be 475 per 100,000 persons in 2020 and 406 per 100,000 people in 2030. This would amount to a reduction of 15.2 % from 2020 if there were no interventions, and other trends do not change from the present day. Under the least optimistic assumptions about contact tracing (only 4.5% of incident TB cases are contacts, our contact screening program reaches 25% of those contacts, averting an average of 2 months of time infectious), we projected that the 2030 incidence would be 406 per 100,000, a 15.2% reduction from 2020 (the same as not having any intervention at all). This represents negligible relative reduction in incidence from contact training. Under the most optimistic assumptions (50% of incident TB cases are contacts, our contact screening program reaches 100% of those contacts, averting an average of 5 months of time infectious), we projected that the 2030 incidence would be 389 per 100,000 a 19.3% reduction from 2020, or 3.6% gain compared to no intervention. Table 3 gives the full spectrum of potential reductions from undertaking contact tracing under a range of assumptions.

Figure 3: Projected TB incidence trends in South Africa s among contacts with infectious duration of 3 months.



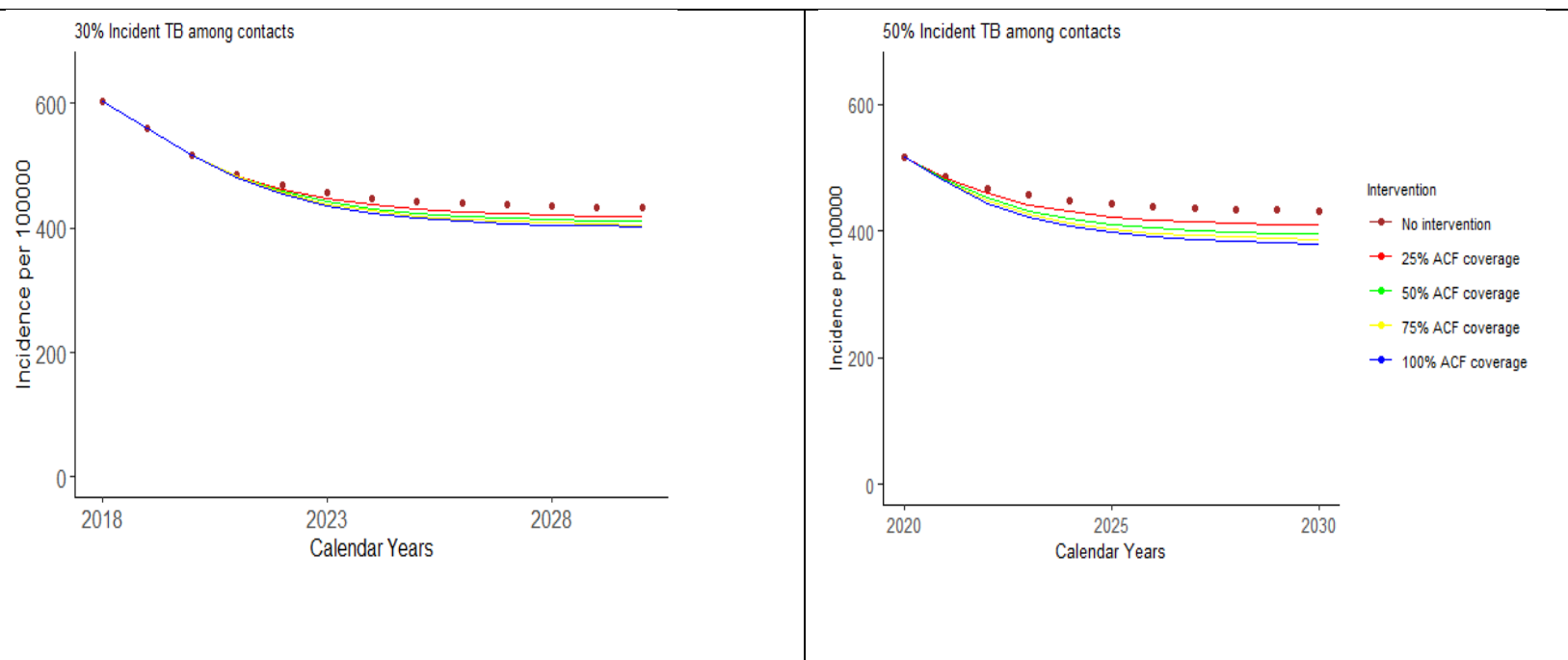
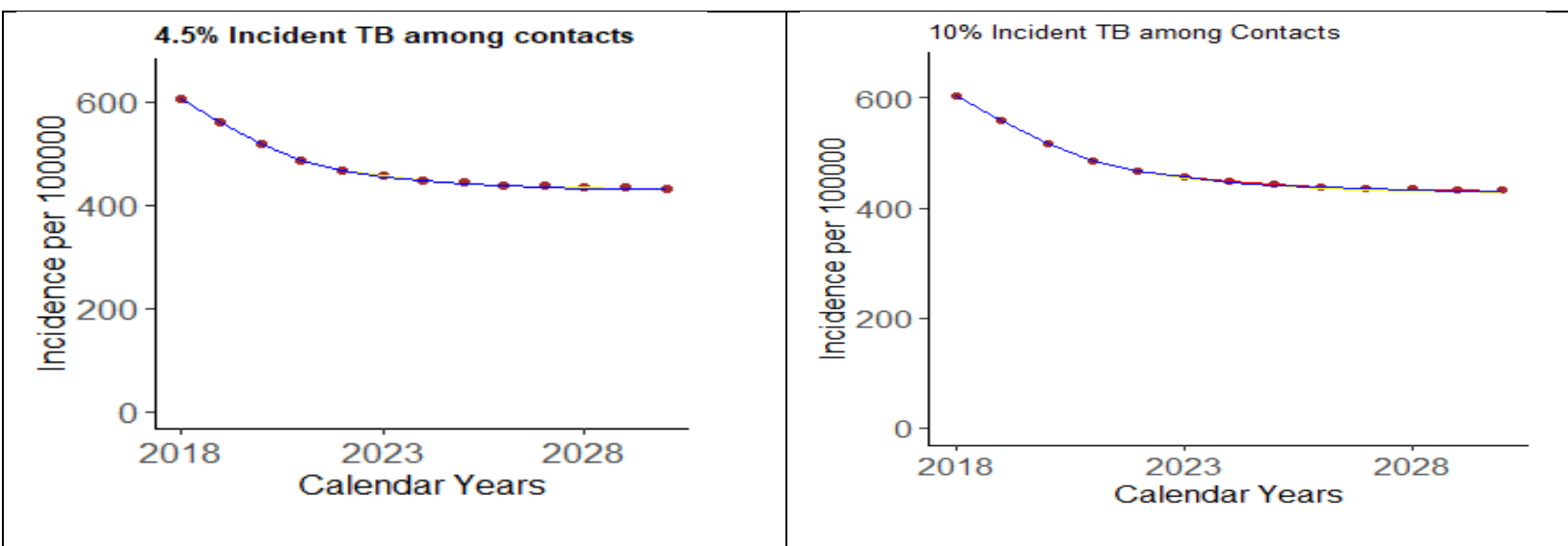


Figure 4 : Projected TB incidence trends in South Africa among contacts with infectious duration of 6 months.



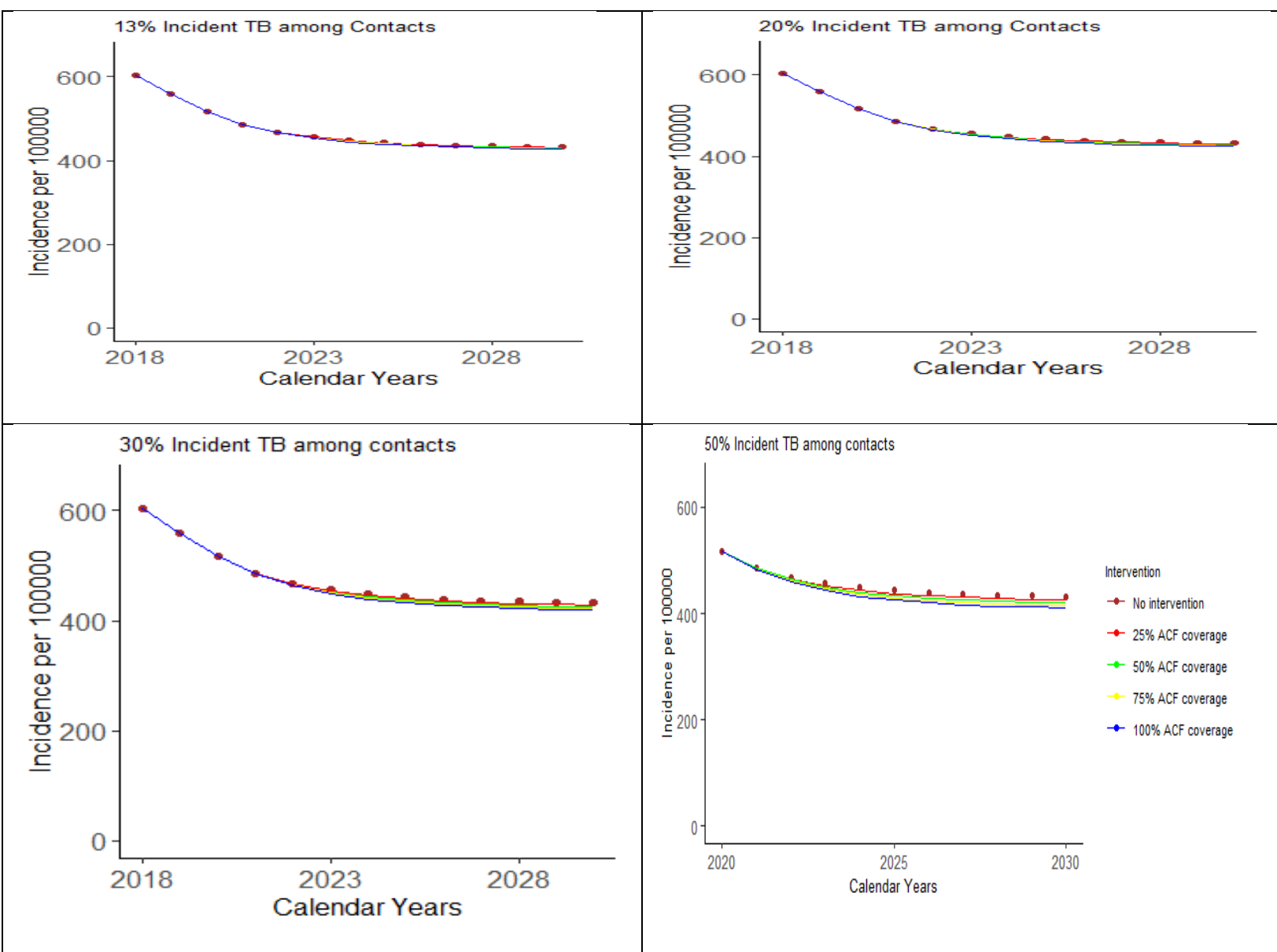


Table 3: Projected Reduction in TB Incidence in 2030 after implementing contact tracing*

A. Contact tracing implemented for 10 years with average infectious time of 3 months

% contacts treated	Proportion of incident cases among contacts					
	4.5%	10%	13%	20%	30%	50%
25%	0.4%	0.8%	1%	1.5%	2.3%	3.8%
50%	0.5%	1.2%	1.5%	2.4%	3.6%	6.2%
75%	0.7%	1.5%	2%	3%	4.5%	7.7%
100%	0.8%	1.7%	2.2%	3.4%	5.2%	8.8%

B. Contact tracing implemented for 10 years with average infectious time of 6 months

% contacts treated	Proportion of incident cases among contacts					
	4.5%	10%	13%	20%	30%	50%
25%	0.1%	0.2%	0.3%	0.4%	0.6%	1%
50%	0.2%	0.4%	0.5%	0.8%	1.2%	2%
75%	0.25%	0.5%	0.7%	1.1%	1.6%	2.8%
100%	0.3%	0.7%	0.9%	1.4%	2%	3.5%

*The percentages in the table above are obtained by subtracting the incidence in 2030 after implementing the intervention from the incidence in 2030 without the intervention and scaling it by dividing it by incidence in 2030 in the no intervention group and expressing it as a percentage.

3.2 Sensitivity Analysis

Sensitivity analysis was performed in a population where the proportion of incident TB cases among contacts was 13% to assess which parameters would affect the projections the most. When the reactivation rates were changed it was noted that the reduction was the same when 2020 values were projected over the next 10 years. There was a mild change in the reduction when the reactivation rates and TB transmission rates were extrapolated from 2020 values or taken at a midpoint between current 2020 value and that of an extrapolated value in 2030. Changing the HIV incidence rate or ART

initiation rate did not seem to affect the results. The influence of changing the TB transmission rate and reactivation rate did not seem remarkable.

The percentages in the table below are obtained by subtracting the incidence in 2030 from the incidence in 2020 and scaling it by dividing it by incidence in 2020 and expressing it as a percentage.

Table 4: Reactivation rate of TB

Reactivation rate extrapolated from 2020 values (2020 value:1.2, 2030 value: 0.9)

% contacts treated	Effective infectious duration 3 months	6 months
25%	0.7%	0.2%
50%	1%	0.3%
75%	1.3%	0.5%
100%	1.5%	0.6%

Reactivation rate projected at same rate as 2020. (2020 and 2030 value: 1.2)

% contacts treated	Effective infectious duration 3 months	6 months
25%	1%	0.3%
50%	1.5%	0.5%
75%	1.9%	0.7%
100%	2.2%	0.9%

Reactivation projected at half as that 2020 and the extrapolated value. (2020: 1.2, 2030: 1.05)

% contacts treated	Effective infectious duration 3 months	6 months
25%	0.8%	0.2%
50%	1.3%	0.4%
75%	1.6%	0.6%
100%	1.9%	0.8%

Table 5: HIV incidence rate

HIV incidence extrapolated from 2020 values (2020 value: 0.004/py, 2030 value: 0.002/py)

% contacts treated	Effective infectious duration 3 months	6 months
25%	0.9%	0.2%
50%	1.4%	0.4%
75%	1.8%	0.6%
`100%	2%	0.8%

HIV incidence projected at same rate as 2020. (2020 and 2030 value 0.004/py)

% contacts treated	Effective infectious duration 3 months	6 months
25%	1%	0.3%
50%	1.5%	0.5%
75%	1.9%	0.7%
`100%	2.2%	0.9%

HIV incidence

projected at a rate half of 2020 and the extrapolated value. (2030:0.003/py)

% contacts treated	Effective infectious duration 3 months	6 months
25%	1%	0.2%
50%	1.5%	0.5%
75%	1.8%	0.7%
`100%	2.1%	0.8%

Table 6: Sensitivity analysis changing the TB transmission rate.

Transmission rate extrapolated from 2020 values (2020 value: 13, 2030 value: 8)

% contacts treated	Effective infectious duration 3 months	6 months
25%	0.8%	0.2%
50%	1.2%	0.4%
75%	1.6%	0.6%
100%	1.7%	0.8%

TB transmission rate projected at same rate as 2020. (2020 and 2030 value: 13)

% contacts treated	Effective infectious duration 3 months	6 months
25%	1%	0.3%
50%	1.5%	0.5%
75%	1.9%	0.7%
100%	2.2%	0.9%

TB transmission in 2030 projected at a rate half as that 2020 and the extrapolated value (2030 value: 10.5)

% contacts treated	Effective infectious duration 3 months	6 months
25%	0.9%	0.3%
50%	1.4%	0.5%
75%	1.7%	0.6%
100%	2%	0.8%

Table 7: ART initiation rate changed

ART initiation rate extrapolated from 2018 rate. (2020 value: 0.34, 2030 value: 0.72)

% contacts treated	Effective infectious duration 3 months	6 months
25%	0.9%	0.3%
50%	1.5%	0.5%
75%	1.8%	0.7%
100%	2.1%	0.9%

ART initiation rate same as 2018 (2020 and 2030 value: 0.34)

% contacts treated	Effective infectious duration 3 months	6 months
25%	1%	0.3%
50%	1.5%	0.5%
75%	1.9%	0.7%
100%	2.2%	0.9%

ART initiation rate half of the 2020 and the extrapolated 2030 value (2030 value: 0.54)

% contacts treated	Effective infectious duration 3 months	6 months
25%	0.9%	0.3%
50%	1.5%	0.5%
75%	1.8%	0.7%
100%	2.1%	0.9%

We then ran a sensitivity analysis by changing the following parameters by 25%: a) treatment coverage and treatment success proportion of TB in SA, b) latent protection factor (LPF), c) case fatality ratio of TB and d) proportion of patients who were on anti-tuberculous therapy in South Africa. Of these, we found that the latent protection factor (tables 8A and 8B) and the treatment coverage rate (tables 11A and 11B) in South Africa were the ones which affected the results the most, while the other two did not change the impact of interventions on incidence by a huge margin. Reduction in the latent protection factor did not impact the reduction in incidence due to our intervention. However, increasing the LPF (i.e proportion of latent TB patients who are re-infected) led to an increase in the impact of the intervention which in turn was proportion to the coverage of ACF (i.e in a setting with higher risk of

reinfection with TB if a higher ACF coverage is achieved , then the intervention can give some impact). Again, this was noticed only in the group which was treated earlier and for those with an average duration of infection of 6 months, there was no impact of intervention between baseline model and increasing the LPF.

Decreasing the current TB coverage of the national program in SA increased the impact of ACF tracing. Increasing the current TB coverage to 95% decreased the impact of our intervention in the 3-month infectious duration group. ACF tracing had a lesser impact than the national TB program when the coverage was set at 95% and the average duration of infection was 6 months. That is because with a 95% coverage proportion of TB patients, the patients started on therapy under the national program earlier than the 6-month period, making this intervention superfluous at that time point. In fact, if ACF was conducted such that the patient was infectious on an average for 6 months then it would perform poorly as compared to the national program with a coverage of 95%.

The percentages in the table below are obtained by subtracting the incidence in 2030 from the incidence in 2020 and scaling it by dividing it by incidence in 2020 and expressing it as a percentage.

The results were as follows:

Table 8A: Latent protection factor (baseline model value was 0.28)

Reducing it by 25% (setting it at 0.21)

% contacts covered	Average infectious duration=3 months	Average infectious duration=6 months
0.25	0.9%	0.2%
0.5	1.4%	0.4%
0.75	1.7%	0.6%
1	2%	0.8%

Table 8 B: Increasing LPF by 25% (setting it at 0.35)

% contacts covered	Average infectious duration 3 months	Average infectious duration 6 months
0.25	1.1%	0.3%
0.5	1.8%	0.6%
0.75	2.2%	0.8%
1	2.5%	1%

Table 9 A: Treatment success proportion (baseline model among HIV negative - 0.82 and HIV positive – 0.72

Reducing the treatment success proportion by 25% in HIV positive and negative groups

% contacts covered	Average infectious duration 3 months	Average infectious duration 6 months
0.25	1%	0.3%
0.5	1.6%	0.5%
0.75	2%	0.7%
1	2.3%	0.9%

Table 9B: Increasing the treatment success proportion by 25% in HIV positive and negative groups.

% contacts covered	Average infectious duration 3 months	Average infectious duration 6 months
0.25	1%	0.3%
0.5	1.6%	0.5%
0.75	1.9%	0.7%
1	2.2%	0.9%

Table 10A: Changing the case fatality ratio for TB (baseline model value was 0.15)

Reducing the case fatality ratio by 25% (0.11)

% contacts covered	Average infectious duration 3 months	Average infectious duration 6 months
0.25	1%	0.3%
0.5	1.6%	0.5%
0.75	2%	0.8%
1	2.3%	1%

Table 10B: Increasing the case fatality ratio by 25% (0.18)

% contacts covered	Average infectious duration 3 months	Average infectious duration 6 months
0.25	1%	0.3%
0.5	1.6%	0.6%
0.75	1.9%	0.8%
1	2.2%	0.9%

Table 11A: Change in TB treatment coverage (baseline 76%)
Reducing the TB treatment coverage by 25% (57%)

% contacts covered	Average infectious duration 3 months	Average infectious duration 6 months
0.25	1.7%	0.8%
0.5	2.4%	1.4%
0.75	2.8%	1.7%
1	3%	2%

Table 11B: the TB treatment coverage by 25% (95%)

% contacts covered	Average infectious duration 3 months	Average infectious duration 6 months
0.25	0.2%	-0.3%
0.5	0.4%	-0.6%
0.75	0.6%	-1%
1	0.8%	-1.5%

The negative values in Table 11B indicate that if 95% coverage with antituberculosis coverage is implemented in the national program, then the national program will reduce the incidence more than contact tracing conducting at 6 months.

4. DISCUSSION:

We used a calibrated population- based model to project the effect of tracing household contacts patients with active tuberculosis in South Africa. Our results suggest that contact tracing in South Africa would help reduce the incidence of tuberculosis to some extent depending on how quickly the contacts are traced and what proportion of incidence TB cases is found in contacts. The impact of household contact investigation depended on the proportion of incident cases occurring among contacts, the average amount of infectious person-time per patients, and the coverage of the intervention among eligible contacts. This suggests that contact tracing is most effective when the proportion of incident cases among contacts is high and when a high proportion of them are treated early. It is worth noting that assuming a contact is detected at 3-months of being infectious duration of a contact, a 25% treatment coverage of contacts where 10% of incident cases are among contacts offers more reduction in incidence as a 100% treatment coverage with 4.5% contacts with incident TB. This suggests that in a high burden setting where the possibility of TB among contacts is higher, there is a benefit to reduction of the incidence using ACF.

We tested our interventions across various percentages of tuberculosis that could be attributed to contacts of TB patients. We tested the interventions where we set the percentage of TB in contacts was at 4%, 10%, 13%, 20% and 30%. Values for TB in contacts of patients has found to range from 1% to 4.5%. (15,16,40,41). So, we think that our simulations which are for the 4% section of active contacts with TB may mimic the ground realities in South Africa more accurately. However, this is a percentage for the entire nation. It is possible in certain areas this proportion may go higher. This implies that the best way that contact tracing may be effective is through early tracing and a higher coverage of treatment among contacts. As noted in Tables 2A to 2C, the reduction of incidence is highest (8.8%) when all the contacts with incident TB are traced within 3 months of becoming infectious. Complete

coverage of all incident cases who are contacts may not be very possible in real life. In that case, timing of tracing becomes crucial. As our simulation shows the earlier the contacts are traced the bigger the drop in incidence. There may even be a rationale for preventive therapy to contacts so that they can be prevented from being infected and therefore infectious (42).

We also noted that the duration of infectiousness averted in contacts also has an impact on the incidence trends. As seen in table 1, irrespective of proportion of incidence of TB among contacts and the proportion covered with anti-tuberculous therapy, allowing an increase in delay of detection by even 3 months leads to the effectiveness of the intervention halving. So, our model suggests that along with a higher proportion of incident cases among contacts, the timing of detection also matters, which informs that a delay of even 3 months can reduce the effectiveness of treatment. This therefore underscores the importance of active case finding through contact tracing in high burden countries. It also emphasizes early detection of TB cases to reduce their average infectious time. This could mean earlier diagnosis of the index case- which can in turn be done by improving access to healthcare.

The WHO has released their screening guidelines which gives certain principles of screening for TB, namely: a) good infrastructure should be in place before screening is initiated; b) high risk groups should be targeted for screening instead of indeterminate mass screening; c) algorithms should be chosen based on accuracy and feasibility; d) screening should be ethical; and e) screening for TB should be combined with other public health delivery systems with f) periodic assessments of screening system (18). The same document strongly recommends screening in household or close contacts and subpopulations with high levels of undetected TB (1% or higher) as well as in subpopulations with poor access to healthcare (18). Our findings are consistent with the WHO guidelines on contact tracing, in that they show greater effectiveness when implemented in a setting where contacts form a higher burden of the TB incident cases and that early detection can help reduce the infective duration.

Studies in Vietnam by Fox et al and the ZAMSTAR trial have showed that case detection rates increased after contact tracing of index TB cases was implemented (14,15) The relative risk was 2.5 for cumulative incidence of tuberculosis in the contact tracing arm as compared to the control arm in the study by Fox et al (14). These studies also imply a higher case burden among contacts which is detected late. Hanrahan et al were unable to show an increased case detection among contacts which ended up showing no difference in incidence rates among the contact tracing and passive case finding arm (16). The authors state that they used Xpert RIF to diagnose TB as opposed to cultures and assume that could have led to a lower detection rate (16). We have not specified any diagnostic method in our simulation. We have assumed that whatever contacts have TB would be diagnosed with a 100% accuracy and treated with a success rate that is proportional to the current rates in South Africa. This may not be a very realistic assumption, and we think that to achieve the 25% rate of covering contacts with TB, a higher proportion may need to be tested to achieve those targets considering the possibility of false negatives.

As Golub et al have noted, ACF is should be based on 1) prevalence of the disease, 2) epidemiological importance, 3) chances of being detected otherwise and 4) cost. South Africa has a high disease burden of TB where contact tracing needs to be implemented to reduce the incidence. As per our model, the epidemiological importance of the ACF is demonstrated by the delay in detection reducing the effectiveness of interventions. Since the anti-tuberculous therapy coverage in South Africa was 76% in 2018 it is evident that early case detection is still an issue (20). Our model also gives a good basis for implementation of ACF based on the criteria provided by Golub et al.

Based on our model we would recommend that contact tracing in areas of high disease burden in South Africa would be a way to start active case finding in South Africa. As noted, incidence reduction is very sensitive to two factors i.e.: proportion of contacts with incident TB and the averted period of

infectiousness. This implies that time is an important component in ACF. So, it is critical that the duration of time when undiagnosed contacts can be infectious should be reduced to the largest extent possible. This may involve incentives or home-based tracking especially in high burden areas or provinces. The intervention can be implemented in phases.

Our model is consistent with the current status of the TB-HIV epidemic in South Africa and the future trends in it. However, the burden of TB is not the same across South Africa and it may differ among communities (43). Our model may not be able to capture these differences, even though it does seem to reflect the overall trend in South Africa. There may be areas in South Africa where contact tracing may give a more significant decrease in TB incidence as compared to other areas not densely populated or with a higher socio-economic status.

We did not assess reinfection in previously treated individuals. Reinfections form a significant burden of TB in South Africa as per Marx et al who showed in a retrospective cohort study that 51% of cases in SA were due to reinfections (44). Drug resistance rates in both HIV and TB may change the prevalence, mortality and the rates of movement from one compartment to another (e.g., successful treatment), and we have not modeled these parameters. The TB and HIV epidemics are fairly correlated in South Africa, and a change in HIV incidence or prevalence can affect the tuberculosis levels.

We also had a very simplified model of contact tracing where the rate of diagnosis was reflected purely by the average duration of infectiousness. We could have modeled a distribution of individual diagnosis rates and a separate duration of infectiousness. We have also constructed the model such that all contacts who are tested for TB and are positive are also started on anti-tuberculous therapy. This may not always be the case. We also assumed that all patients who were HIV positive and found to have TB were started on ART as well within the same year. This, while true on a policy level may not be true in real life. Our incidence rate of MTCT infections of HIV may also be on the higher side considering that we are basing

it on current incidence estimates and that as the population on ART grows, this number may reduce over time.

5.CONCLUSION

Our model shows that contact tracing may help in reducing the incidence of TB in South Africa if contacts are traced early in their illness and close contacts account for a substantial proportion of all incident TB. This model is most susceptible to changes in the proportion of patients under coverage for anti TB therapy where if the proportion increases, it becomes more effective than the intervention and a decrease in the proportion of treatment coverage improves the intervention's impact.

8. BIBLIOGRAPHY

1. World Health Organisation. World Health Organisation. Global tuberculosis report 2018 . 2019.
2. World Health Organisation. World Health Organisation. The End TB strategy. 2015.
3. UNAIDS. UNAIDS Data [Internet]. 2018. Available from: <http://aidsinfo.unaids.org/>
4. World Health Organisation. World Health Organisation. Global tuberculosis report 2017. 2018.
5. Hansoti B, Mwinnyaa G, Hahn E, Rao A, Black J, Chen V, et al. Targeting the HIV Epidemic in South Africa: The Need for Testing and Linkage to Care in Emergency Departments. *EClinicalMedicine*. 2019;15:14–22.
6. Adetifa IM, Kendall L, Bashorun A, Linda C, Omoleke S, Jeffries D, et al. A tuberculosis nationwide prevalence survey in Gambia, 2012. *Bull World Health Organ*. 2016;94(6):433–41.
7. Hoa NB, Sy DN, Nhung NV, Tiemersma EW, Borgdorff MW, Cobelens FG. National survey of tuberculosis prevalence in Viet Nam. *Bull World Health Organ*. 2010;88(4):273–80.
8. Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet*. 2010;376:1244–53.
9. Sung CK. Case-finding in the Korean national tuberculosis programme. *Bull Int Union Tuberc*. 1976;(51):381–2.
10. Gothi GD, Narayan R, Nair SS, Chakraborty AK, Srikan-taramu N. Estimation of prevalence of bacillary tuberculosis on basis of chest X-ray and-or symptomatic screening. *Indian J Med Res*. 1976;(64):1150–9.
11. Arabin G, Gartig D, Kleeberg HH. First tuberculosis prevalence survey in Kwazulu. *Afr Med J*. 1979;(56):434–8.
12. National Institute for Health and Care Excellence (UK). Tuberculosis: Prevention, Diagnosis, Management and Service Organisation. London, UK; 2016. Report No.: NICE Guideline, No. 33.
13. Miller AC, Golub JE, Cavalcante SC, Durovni B, Moulton LH, Fonseca Z et al. Controlled trial of active tuberculosis case finding in a Brazilian favela. *Int J Tuberc Lung Dis*. 2010;14:720–6.
14. Fox GJ, Nhung NV, Sy DN, Hoa NLP, Anh LTN, Anh NT, et al. Household-Contact Investigation for Detection of Tuberculosis in Vietnam. *N Engl J Med*. 2018;378(3):221-9. *N Engl J Med*. 2018;378(3):221–9.
15. Ayles H, Muyoyeta M, Du Toit E, Schaap A, Floyd S, Simwinga M, Shanaube K, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. . *Lancet*. 2013;382:1183-94. *Lancet*. 2013;382:1183–94.

16. Hanrahan CF, Nonyane BAS, Mmolawa L, West NS, Siwelana T, Lebina L, et al. Contact tracing versus facility-based screening for active TB case finding in rural South Africa: A pragmatic cluster-randomized trial (Kharitode TB). *PLoS Med.* 2019;16(4):e1002796.
17. Kranzer K, Lawn SD, Meyer-Rath G, Vassall A, Raditlhalo E, Govindasamy D et al. Feasibility, yield, and cost of active tuberculosis case finding linked to a mobile HIV service in Cape Town, South Africa: a cross-sectional study. *PLoS Med.* 2018;9(8):e1001281.
18. World Health Organisation. World Health Organisation. Systematic screening for active tuberculosis: principles and recommendations. 2013.
19. Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis.* 8(6):359–68.
20. Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. *Int J Tuberc Lung Dis.* 2005;9(11):1183–203.
21. Dowdy DW, Basu S, Andrews JR. Is passive diagnosis enough? The impact of subclinical disease on diagnostic strategies for tuberculosis. 2013. 2013;187(5):543–51.
22. Naidoo P, Theron G, Rangaka MX., Chihota VN., Vaughan L, Brey ZO et al. The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. *J Infect Dis.* 2017;216((suppl_7)). *J Infect Dis.* 2017;216:suppl 7.
23. Dowdy DW, Chaisson RE, Moulton LH, Dorman SE. The potential impact of enhanced diagnostic techniques for tuberculosis driven by HIV: a mathematical model. *AIDS.* 2006;20(5):751–62.
24. World Bank. World Bank. Rural population (% of total population). [Internet]. World Bank; 2018. Available from: [https:// data.worldbank.org/indicator/SP.RUR.TOTL.ZS](https://data.worldbank.org/indicator/SP.RUR.TOTL.ZS).
25. Blaser N, Zahnd C, Hermans S, Salazar-Vizcaya L, Estill J, Morrow C, Egger M et al. Tuberculosis in Cape Town: An age-structured transmission model. *Epidemics.* 2016;14:54–61.
26. Vynnycky E FP. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. 1997;119(2):183–201. *Epidemiol Infect.* 1997;119(2):183–201.
27. Kiazzyk S BT. Latent tuberculosis infection: An overview. *Can Commun Rep.* 2017;43(3–4):62–6.
28. Asiimwe SB, Kanyesigye M, Bwana B, Okello S, Muyindike W. Predictors of dropout from care among HIV-infected patients initiating antiretroviral therapy at a public sector HIV treatment clinic in sub-Saharan Africa. *BMC Infect Dis.* 2016;16(43). *BMC Infect Dis.* 2016;16(43).
29. Žaba B, Marston M, Crampin A, Isingo R, Biraro S, Bärnighausen T, et al. Age-specific mortality patterns in HIV-infected individuals: a comparative analysis of African community study data. *AIDS.* 2007;21:S87–96.

30. Soetaert K, Petzoldt T, Setzer RW. Solving Differential Equations in R: Package deSolve. *J Stat Softw.* 33(9):1–25.
31. World Health Organisation. Tuberculosis profile- South Africa [Internet]. TB country profile. [cited 2020 Mar 5]. Available from: https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=ZA&LAN=EN&outtype=html
32. World Health Organisation. Global Health Repository [Internet]. Available from: <https://apps.who.int/gho/data/node.country.country-ZAF?lang=en>
33. Nglazi MD, Bekker LG, Wood R, Kaplan R. The impact of HIV status and antiretroviral treatment on TB treatment outcomes of new tuberculosis patients attending co-located TB and ART services in South Africa: a retrospective cohort study. *BMC Infect Dis.* 2015;15:536.
34. Blower, S, Mclean, A, Porco, T et al. The intrinsic transmission dynamics of tuberculosis epidemics. *Nat Med.* 1995;1:815–21.
35. Dalal RP, MacPhail C, Mqhayi M, Wing J, Feldman C, Chersich MF et al. Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in Johannesburg, South Africa. *J Acquir Immune Defic Syndr.* 2008;47(1):101–7.
36. Straetemans, M., Glaziou, P., Bierrenbach, A. L., Sismanidis, C., & van der Werf, M. J. Assessing tuberculosis case fatality ratio: a meta-analysis. *PLoS One.* 2011;6(6):e20755.
37. Jung IY., Rupasinghe D., Woolley I., O'Connor C C., Giles M, Azwa, RI., et al. Trends in mortality among ART-treated HIV-infected adults in the Asia-Pacific region between 1999 and 2017: results from the TREAT Asia HIV Observational Database (TAHOD) and Australian HIV Observational Database (AHOD) of IeDEA. *J Int AIDS Soc.* 2019;22(1):e25219.
38. Masiira B, Baisley K, Mayanja B, Kazooba P, Maher D, Kaleebu P. Mortality and its predictors among antiretroviral therapy naïve HIV-infected individuals with CD4 cell count ≥ 350 cells/mm³ compared to the general population: Data from a population-based prospective HIV cohort in Uganda. *Glob Health Action.* 2014;7(21843).
39. Horsburgh CR, Jr O'Donnell M, Chamblee S., Moreland J L., Johnson J., Marsh B J., Narita M., Johnson L S., & von Reyn CF. Revisiting rates of reactivation tuberculosis: a population-based approach. *Am J Respir Crit Care Med.* 2010;182(3):420–5.
40. Martin-Sanchez M, Brugueras S, de Andrés A, Simon P, Gorrindo P, Ros M, et al. Tuberculosis incidence among infected contacts detected through contact tracing of smear-positive patients. . *PLoS ONE.* 2019;14(4):e0215322.
41. Reichler MR., Khan A., Sterling TR., Zhao H, Moran J, McAuley J et al. Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team Risk and Timing of Tuberculosis Among Close Contacts of Persons with Infectious Tuberculosis. *J Infect Dis.* 2018;218(6):1000–8.

42. Marx FM, Yaesoubi R, Menzies NA, Salomon JA, Bilinski A, Beyers N, Cohen T. Tuberculosis control interventions targeted to previously treated people in a high-incidence setting: a modelling study. *Lancet Glob Health*. 2018;6(4):e426–35.
43. Annabel K. TB Statistics South Africa - National, incidence, provincial [Internet]. [cited 2020 Mar 19]. Available from: <https://tbfacts.org/tb-statistics-south-africa/>
44. Marx MF, Dunbar R, Enarson DA, Williams BG, RM, der Spuy GD, van Helden PD, Beyers N. The Temporal Dynamics of Relapse and Reinfection Tuberculosis After Successful Treatment: A Retrospective Cohort Study,. *Clin Infect Dis*. 2014;58(12):1676–83.

9. CURRICULUM VITAE

ACADEMIC QUALIFICATIONS:

- **Masters in Epidemiology** **Expected graduation year:**
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- **MBBS, Christian Medical College, Vellore, India.** **March**
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RESEARCH EXPERIENCE and TEACHING EXPERIENCE:

RESEARCH ASSISTANT AT JOHNS HOPKINS SCHOOL OF PUBLIC HEALTH: 2018- Present

- ARIC study on Stroke Severity – data abstraction, proposal and manuscript writing.
- Department of Medicine: Primary Care Cancer Survivorship Study- data abstraction and data management
- Department of Medicine: Medical Students Mental Wellbeing Study- data abstraction, data management, data analysis and manuscript writing.
- International Vaccine Access Centre: Literature Review for a grant proposal to the World Health Organisation

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- Biostatistics: Summer Institute (2019), Statistical Methods in Public Health (621), Winter Institute (2020)
- Epidemiology: Principles of Epidemiology (601), Fundamentals of Epidemiology, Outbreak Investigations (1st Term and Summer Institute), Epidemiologic Inference in Public Health II (722).
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Consultant Physician and Medical Superintendent **June 2015-Aug**
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Emmanuel Hospital Association, New Delhi, India

- Clinical care in the Emergency, Intensive Care Unit and the wards
- Implemented clinical and quality control protocols in the wards and laboratories
- Currently pursuing projects on Imazethaphyr and hair dye ingestion.
- Implemented and oversaw community projects in mental health
- Conducted Continuing Medical Education seminars for doctors and nurses in the organisation.

Assistant Professor, Medicine and Infectious Diseases,

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- Clinical work in the departments of internal medicine and infectious diseases esp. HIV, TB and tropical diseases in South Asia's premier teaching hospital.
- Undergraduate and postgraduate bedside teaching and didactic lectures.
- Organised Clinical Infectious Diseases Society CME for 2 years.
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Publications in Peer reviewed journals:

1. **Shalom Patole**, Ramya I Bilateral renal vein thrombosis due to factor VIII deficiency: First case report from India *J Assoc Physicians India*. 2015;63(8):87-8.
2. **Shalom Patole**, Burza S, Varghese GM Multiple relapses of visceral leishmaniasis in a patient with HIV in India: a treatment challenge. *Int J Infect Dis*. 2014 204-6.
3. Janardhanan J, **Shalom Patole**, Varghese L, Rupa V, Tirkey AJ, Varghese GM. Elusive treatment for human rhinosporidiosis. *Int J Infect Dis*. 2016 ;48:3-4.
4. Choi Y, Radhakrishnan A, Mahabare D, **Shalom Patole**, Dy SM, Pollack CE, et al .The Johns Hopkins Primary Care for Cancer Survivor Clinic: lessons learned in our first 4 years. *J Cancer Surviv*. 2019 Oct 24. doi: 10.1007/s11764-019-00816-3.
5. Mohamad Gouse, Viswanath Jayasankar, **Shalom Patole**, Balaji Veeraraghavan, and Manasseh Nithyananth Clinical Outcomes in Musculoskeletal Involvement of *Burkholderia Pseudomallei* Infection *Clin Orthop Surg*. 2017 Sep;9(3):386-91.
6. Kundavaram Paul Prabhakar Abhilash, **Shalom Patole**, Mohan Jambugulam, Sowmya S, Shubhankar Mitra, et al Changing profiles of infective endocarditis in India: A South Indian experience. *Journal of Cardiovascular Disease Research*, 2017; 8(2): 56-60
7. Abhilash KP, Gunasekaran K, Mitra S, **Shalom Patole**, Sathyendra S, Jasmine S, et al Scrub typhus meningitis: An under-recognized cause of aseptic meningitis in India. *Neurol India*. 2015;63(2):209-14

8. Letter to the Editor Binila Chacko, John Victor Peter, **Shalom Patole**, Jude Joseph Fleming, Ratnasamy Selvakumar *Indian J Crit Care Med.* 2011;15(3):196-7
9. Binila Chacko, John Victor Peter, **Shalom Patole**, Jude Joseph Fleming, Ratnasamy Selvakumar Electrolytes assessed by point-of-care testing – Are the values comparable with results obtained from the central laboratory? *Indian J Crit Care Med.* 2011;15(1):24-9
10. Victor Peter J, **Shalom Patole**, Fleming JJ, Selvakumar R, Graham PL Agreement between paired blood gas values in samples transported either by a pneumatic system or by human courier. *Clin Chem Lab Med.* 2011;49(8):1303-9

Poster Presentations:

A profile of drug resistant tuberculosis in a tertiary centre in South India Shalom Patole, Kirti Sabnis, Joy Michael, George Varghese, Priscilla Rupali. 4th Annual Conference of the Clinical Infectious Diseases Society 2014, Bangalore

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